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CME Review

Advances in diagnosis and management of insect sting allergy

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At the conclusion of this activity, participants should be able to:

- Interpret the results of new and existing diagnostic tests for insect sting allergy
- Recognize clinical and laboratory markers of risk for severe reactions to stings
- Recommend the most appropriate dose, regimen and duration for venom immunotherapy

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Introduction

Insect sting allergy affects more than 5% of the population and is amenable to relatively easy diagnosis and treatment, yet it remains an enigma in many ways. Difficulties arise primarily from lack of

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Table 1
Diagnostic evaluation of insect sting allergy

Variable	History	Skin test	Specific IgE	BAT	Recombinant allergen	RAST inhibition	Tryptase baseline
Diagnosis							
No reaction	X						
LLR	X						
Mild SR	X	X	X				
Anaphylaxis	X	X	X	X	X	X	X
Predict severe reaction (to stings or VIT)	X			X			X
Cross-reactivity (HB/YJ)					X	X	
Discontinue VIT	X			X			X

Abbreviations: BAT, basophil activation test; HB, honeybee; LLR, large local reaction; SR, systemic reaction; VIT, venom immunotherapy; YJ, yellow jacket.

tests that accurately predict the outcome of a future sting. After decades of investigation, we are much more aware of the natural history of venom sensitization and the clinical expression of sting reactions. We can assign relative risk to an increasing number of factors. Remarkably, the single best predictor of the outcome of a future sting is still the history of reaction to a previous sting. It is therefore important to integrate the detailed history of sting reaction with the statistical predictions of many factors and a knowledge of the natural history of the condition. The historical background and clinical evidence base for our diagnosis and treatment were published in the 1970s and 1980s and have been extensively reviewed.[1] The most recent update of the Practice Parameters on Insect Hypersensitivity reflects continuing growth in the field, not only in the refinement of diagnostic tests and the protocols for treatment but also in the area of clinical judgment as it enters into so many of the decisions we make with our patients.[2] Some of these important decisions include when (and whether) to do any diagnostic tests, whether to prescribe an epinephrine injector, whether to start venom immunotherapy (VIT) (and with what dose and regimen), whether and when to stop VIT, and what to do about other risk factors (eg, medications and underlying conditions).

Epidemiology

Insect sting allergy is not rare, with a history of systemic reaction to sting in 1% of children and 3% of adults. In addition, another 5% or more state that they have had abnormally large or prolonged swelling at the site of the sting (large local reaction). Sensitization to Hymenoptera venom, on the other hand, is common, with positive skin or serum test results for venom specific IgE in 20% or more of adults and 30% to 40% in the weeks after a sting. Such asymptomatic venom sensitivity is often transient, disappearing in most patients after a few years. However, when it persists, venom sensitization is associated with an estimated 15% chance of systemic reaction to a subsequent sting. As with other allergens, the presence of venom specific IgE is necessary but not sufficient for systemic reactions to stings.

Diagnostic Testing

The purposes of diagnostic tests are to confirm allergic sensitization to venom and to help define the risk of future systemic reaction to stings. With few exceptions, individuals who have not had systemic reactions do not need to be tested for venom allergy. In patients with a history of systemic reactions to stings, the frequency of systemic reactions to subsequent stings is correlated with the severity of the previous reactions. In a study using challenge stings, systemic reactions occurred in more than 40% of those with previous severe reactions but only 23% in those with previous moderate systemic reactions and 17% in those with mild (cutaneous) systemic reactions.[3] In that same study, a marked difference was found in the chance of systemic reaction between the 2 most common species of yellow jacket. This is clinically relevant, for example, when a patient gives a history of severe reaction to a sting but with no reaction to a subsequent sting, because a different species could potentially cause a severe reaction again. The clinical utility of various methods of diagnostic testing is summarized in Table 1.

Venom skin (or serum IgE) tests also show a correlation with the frequency of systemic reactions to stings, with the highest chance of reaction in patients with the strongest positive skin test results and the lowest chance of reaction in those with negative skin test results but positive serum IgE test results. However, the level of sensitivity on skin or serum tests does not reliably predict the severity of a sting reaction. An accurate screening test is sorely needed, especially because half of fatal sting reactions occur in individuals with no prior history of a sting reaction. However, the frequency of asymptomatic sensitization greatly increases the chance that testing without prior probability could lead to unnecessary precautions or treatment.

A surprising proportion (up to 30% in several large studies) of people with a history of systemic reaction to a sting have negative venom skin test results. However, many of these individuals have positive serum IgE test results, leaving approximately 15% of history-positive patients with no detectable venom specific IgE. In sting challenge studies, only approximately 6% of such individuals have a systemic reaction to a challenge sting.[4] There are many potential reasons for venom skin test results to be negative despite a convincing history. The test results can be negative in 20% to 50% of patients during the refractory period soon after a sting reaction but are positive 4 to 6 weeks after the sting. Another possible problem is the inherent variability of venom skin tests, which can reveal a 10-fold increase or decrease in the concentration for a positive result when performed weeks or months apart.[5] The clinical implication is the potential to omit a venom in treatment when a subsequent test could have a positive result. The limited predictive value of the available diagnostic tests has spurred the development of new methods and materials for improved accuracy.

Given the limited positive predictive value of venom tests, one must consider very carefully the potential consequences of a positive test result and the relative indication to perform the test. The relative risk of a severe reaction can be estimated from the history of previous reactions. Diagnostic tests are clearly indicated in those at high risk for reactions but should be avoided in low-risk individuals. It is a fallacy to think that performing the tests will help to make the clinical decision about starting VIT. In fact, the opposite can be true in that a positive test result in a low-risk individual will often create increased fear of reaction even though the history might indicate less than a 3% chance of needing epinephrine after a sting. The clinician should have a thorough discussion with the patient before the test is even performed about what the clinical recommendation will be and to discourage testing when the history indicates that VIT is not necessary.

There have been 2 advances in diagnostic methods that show promise for improved accuracy and clinical significance in testing for insect venom allergy. Basophil activation tests have been proposed for diagnosis of many hypersensitivity reactions, even those that are not IgE mediated, based on the capacity of the allergen to induce either mediator release or expression of activation markers on the patient's basophils. Although there have been varying methods used to express the results of these tests, there is accumulating evidence that they can be markers for a number of clinically significant outcomes. Basophil activation tests were more sensitive than intradermal skin tests in patients with negative serum IgE and skin prick test results[6] and predicted the risk of

systemic reactions to VIT.[7] Basophil expression of CD63 was higher in patients who did not respond to VIT (treatment failure),[8] correlated with the protective immune response to honeybee (HB) VIT in children,[9] and was predictive of HB sensitivity after VIT (clinical relapse).[10] There remain inconsistencies in the performance, analysis, and interpretation of basophil activation tests, but when these are standardized, basophil activation tests promise to be a valuable addition to our diagnostic capabilities.

The use of recombinant venom allergens for diagnosis also presents potential advantages, particularly the ability to distinguish cross-reactivity of HB and vespid sensitivity from dual specific sensitization. The cross-reactivity is often attributed to cross-reacting carbohydrate determinants, which are not expressed on recombinant proteins, thus eliminating the cross-reactivity.[11] However, for optimal sensitivity, it may be necessary to include multiple allergens in the reagents.[12] Studies in late 2012 confirmed the utility of the recombinant allergens but questioned the role of cross-reacting carbohydrate determinants.[13] The recombinant vespid venom allergens have more than 90% of the activity of the native protein, but recombinant Api m 1 has shown widely variable activity that may depend on the particular method and source of the recombinant protein.[14,15] It remains to be seen whether the pattern of sensitization to specific allergen components is predictive of the clinical outcome from a sting.

When To Recommend VIT

The indication for VIT, simply stated, is a history of a systemic reaction to a sting and positive venom skin (or serum) test result. However, the frequency of systemic reactions in such patients has been reported to be between 25% and 75%. Many individuals who have venom IgE have a low risk of systemic reaction, including people without a history of an allergic reaction to stings (asymptomatic sensitization), those with large local reactions to stings, and those with only mild (cutaneous) systemic reactions. The difficulty in counseling these patients (particularly if tests are performed and the results are found to be positive) is that the mere presence of venom IgE is associated with at least a 5% to 10% chance of systemic reaction, so the risk will never be zero. What level of risk might justify VIT therefore becomes a matter not only of medical judgment but also of the relative effect on quality of life. In this respect, VIT improved quality of life and epinephrine prescription did not, not only in severe reactors but also in dermal reactors (large local or cutaneous systemic).[16,17]

Low Risk

Large local reactions to stings are IgE-mediated late-phase inflammatory reactions that can be debilitating and may require corticosteroid treatment. Despite the presence of significant levels of venom IgE, the chance of subsequent systemic reactions to stings is relatively small, in the range of 5% to 10% (most of which will not be severe). Venom immunotherapy is therefore not considered to be necessary for large local reactors. However, patients who have unavoidable exposure to stings and require steroid treatment for severe local reactions every year may welcome an effective method of prevention. VIT was not even thought to be effective for large local reactions until 2 reports emerged. Severino et al[18] reported that sublingual immunotherapy (SLIT) with HB venom significantly reduced the size of large local reactions, but a commentary by the European Academy of Allergology and Clinical Immunology Hymenoptera Interest Group pointed out that almost 50% of the patients in the study had no improvement and that SLIT with venom might be too risky for systemic reactors. Golden et al[19] reported a 4-year study that began with a comparison group of untreated controls and showed a significant reduction of the mean size and duration of the local reaction to a sting challenge after 7 to 11 weeks of VIT. The controls were then crossed over to VIT, and the response during 2 to 4 years in the whole group revealed a mean of 70% improvement, with at least 50% improvement in 100% of patients.

In children with cutaneous systemic reactions, the chance of a worse reaction to a future sting is estimated to be less than 3%.[20] In adults, concern about reports of progression to severe reactions has justified recommendations for VIT in the United States. There are 2 retrospective studies that support this concern.[21,22] However, in 2 prospective studies with sting challenge of predominantly mild and moderate systemic reactors, there was only a 1% incidence of systemic reactions more severe than previous sting reactions.[3,23]

High Risk

One of the most established high-risk factors for severe sting reactions is prior severe sting reactions. Even 10 to 20 years after a severe reaction, the chance of systemic reaction to a sting continues to be up to 70% in adults and 30% in children.[20,24] Although patients with more strongly positive venom IgE skin or serum test results have a higher chance of systemic reaction to a sting, there is not necessarily a higher chance of a more severe reaction. A higher risk for severe reaction has also been associated with very rapid onset of reaction, the absence of cutaneous signs, and more advanced age.[25]

Evidence is accumulating that an elevated baseline serum tryptase level (>11.4 ng/mL) is associated with an increased risk of severe reaction to sting, increased chance of systemic reactions to VIT or failure of VIT, and increased chance of relapse or fatal reaction to stings after stopping VIT.[26,27] A large multicenter study found a linear correlation between the baseline tryptase level and the odds ratio for severe sting anaphylaxis.[27] An elevated baseline tryptase level occurs in approximately 10% of patients with systemic reactions to stings and in up to 25% of those with hypotensive reactions.[28] Elevated baseline tryptase is often an indicator of underlying mast cell disorders, including mastocytosis.[26] In fact, insect sting anaphylaxis is one of the most common presenting signs of indolent systemic mastocytosis.[29] In the past, VIT was considered too risky and of questionable benefit in patients with mastocytosis. Subsequent studies found protection that is quite good (75%) but not as reliable as in other patients (85%-95%) and a frequency of systemic adverse reactions somewhat higher (15%-25%) than in other patients (10%-15%).[30] It is likely that elevated baseline levels of other mast cell mediators are also predictive of increased risk of severe or fatal reactions. Thus far, this has only been demonstrated for platelet-activating factor (PAF) in a study by Vadas et al[31] that found that deficiency of PAF-acetylhydrolase is the underlying cause of elevated baseline PAF and increased risk of fatal anaphylaxis.

Venom Immunotherapy

Initial VIT

The decision to initiate VIT is based on the history, diagnostic tests, and presence or absence of high-risk factors for severe reaction.[2] The chance of severe reaction is highest in patients who had previous severe reactions to stings and those with elevated baseline serum tryptase level, HB allergy, or underlying medical conditions. Patients with mild (cutaneous) or moderate systemic reactions to stings (mild airway or hypotensive symptoms not impairing activity) can certainly have more severe reactions to subsequent stings (marked dyspnea or shock), but the need for VIT depends on whether that chance is less than 5% (as in 2 prospective studies) or 20% ot 30% (as in 2 retrospective studies). In much of the world, cutaneous systemic reactions are not considered a clear indication for VIT.[32] Still, there can be a significant impairment in quality of life

for dermal reactors, and the benefit of VIT must be considered. Conversely, not all children are at low risk. Long-term follow-up revealed that children who had moderate to severe reactions still had up to a 30% chance of systemic reaction up to 20 years later.[20] This finding suggests that an adult with a childhood history of severe sting reaction should be tested and, if the result is positive, treated with VIT. Even when the patient has been stung in between without reaction, the risk remains because the sting could have been a different genus or species of insect, and even in the same species there can be a 10-fold variation in the amount of venom injected by the sting.

Dose and Regimen

The starting dose on the first day of the build-up stage is often very small (approximately 0.01 μg). One study found it safe to begin with a starting dose of 1 μg, with no systemic reactions observed in 730 injections, but 1.7% had systemic reactions at doses of 3 to 6 μg, 2.3% at doses of 10 to 50 μg, and 5% with doses of greater than 50 μg.[33] We have had the same experience during the past 30 years in hundreds of patients treated at Johns Hopkins with our standard regimen that begins with 1 to 6 μg on the first day.

Many regimens have been studies for the build-up stage of VIT, including standard/traditional (15-20 weeks), modified rush (6-8 weeks), rush (2-3 days), and ultrarush (3-6 hours) regimens. Although there is clearly increased risk of systemic reaction with ultrarush regimens, rush regimens are reasonably safe, and modified rush regimens are as safe as traditional regimens.[34,35] Rush regimens can be useful when it is too inconvenient for the patient to present for an extended series of weekly treatments, such as when patients live at some distance from the treating center or when they cannot be absent from professional activities (including military). Rush and ultrarush regimens have been successful in patients unable to build up to maintenance dose because of repeated systemic reaction.[35]

The immune response and clinical efficacy of venom immunotherapy are dose dependent. The standard 100-μg maintenance dose is not necessarily optimal for all patients. Complete protection from systemic reaction to a sting occurs in 98% of patients treated with mixed vespid venoms (300-μg total dose), in 90% to 95% of patients treated with single vespid venoms, and in 75% to 85% of those treated for HB allergy.[32] Patients who have reactions to stings during VIT can be protected by increasing the dose to 200 μg.[36] The maintenance dose in children has always been recommended to be the same as in adults, but 2 studies have provided evidence that a 50-μg maintenance dose in children is effective using HB venom and yellow jacket venom, including the long-term outcome after finishing a course of VIT.[37,38]

Medications

The use of medications during VIT can have a positive or negative effect. Blockade of histamine$_1$ (H_1) receptors helps to reduce local and even mild systemic reactions and may act through H_1-receptors on a variety of immunoregulatory cells to enhance the efficacy of VIT.[39] In one study, montelukast was more effective than H_1- blockers at reducing the intensity and duration of large local reactions.[40] On the other hand, some medications may increase the risk of anaphylactic reactions to VIT. Practice parameters recommend avoiding β-blockers during immunotherapy, but one large study found no increased risk of reaction.[25] Muller and Haeberli[41] reported minimal risk for β-blockers in VIT and often increased cardiovascular risk if use of the β-blockers is discontinued. It is unknown whether the risk with β_1-selective β-blockers is less than that observed with the nonselective β-blockers. The risk of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers is less clear. Although some studies have found an increased risk of reaction to stings or VIT, others have not.[25,27] It has also been difficult to evaluate potential differences in risk between ACE inhibitors and angiotensin receptor blockers. The Food and Drug Administration–approved product package insert for Hymenoptera venom extracts states that "relative contraindications include…treatment with beta-adrenergic antagonist drugs or angiotensin inhibitors" and that "ACE inhibitors should be stopped at least 24 hours prior to injection."

Maintenance VIT

The onset of protection with VIT is quite rapid. Sting challenge studies have found that protection against systemic reactions is achieved when the maintenance dose is reached after an 8-week build-up regimen.[42] The maintenance dose is then repeated every 4 weeks for 12 to 18 months, then every 6 weeks for 12 to 18 months, and then every 8 weeks for 12 to 18 months, at which time clinical review is needed to determine whether to discontinue treatment after 5 years. The safety and efficacy of a 12-week interval after the first few years of treatment have been confirmed.[43] It was also shown that a 6-month interval does not maintain adequate protection.

Problems During VIT

Large local reactions to VIT are common and should rarely interfere with achieving the maintenance dose, especially with premedication. Systemic reactions are not uncommon but are usually mild and require only a temporary adjustment of the dose schedule (as with any immunotherapy). Repeated systemic reactions can be addressed in a number of ways. It may be necessary to limit treatment to a single venom initially and to give several small doses at 30-minute intervals to achieve a higher total dose for each visit. Rush venom immunotherapy has been successful in patients with repeated systemic reactions to VIT. There have been a small number of reported cases using omalizumab pretreatment to facilitate VIT up to maintenance doses in patients previously unable to tolerate VIT.[44,45] In most such cases the omalizumab therapy could be safely discontinued after 6 months. Treatment failure (systemic reaction to a sting on VIT) occurs in 5% to 25% of patients, more in HB than in vespid allergic patients. Increasing the maintenance dose to 200 μg can provide full protection in such patients.

Mechanisms of VIT

Venom immunotherapy has been a model for the study of the mechanisms of allergen immunotherapy. Early studies demonstrated the role of increased interleukin 10 (which correlates with IgG4 production) and allergen-specific regulatory T cells. Further investigation revealed that specific T-cell populations (CD4+/CD25+/Foxp3+ T-regulatory cells) suppress allergic responses to venom.[46] One report found changes in the expression of surface molecules (increased CD40 and decreased TLR2) on dendritic cells during VIT, which may contribute to the efficacy of VIT.[47] Also, new clinical studies have elucidated new mechanisms for an old player—IgG blocking antibodies. These antibodies not only block antigen binding to IgE on mast cells but also play an important role in facilitating antigen binding to B cells and T cells.[48] The persistence of the IgG4 antibodies with facilitating antigen binding activity seems to reflect the tolerogenic effects of immunotherapy. However, there is no specific test that is able to accurately predict, in an individual patient, the outcome of a sting before or after VIT.

When to Stop VIT

The decision to stop VIT involves many of the same issues as the decision to begin VIT, particularly the natural history and our ability to predict the chance of a systemic reaction, especially a severe

reaction, to a sting. There are demonstrable advantages to 5 years of VIT compared with 3 years, but some patients, especially children, seem to do well with only 3 years of VIT.[49] In adults who had at least 5 years of maintenance VIT before stopping, there is a 10% chance of systemic reaction to every sting, even 13 years after stopping VIT.[50] For patients who get stung several times in a period of years, the cumulative risk of systemic reaction is 17% or more. However, the reactions that do occur are generally much milder than the pre-VIT sting reaction. In children, VIT with a median duration of 3.5 years resulted in only 5% relapse rate during a 10- to 15-year period.[20] This is better than the outcome in adults and perhaps the most successful long-term tolerance induction by specific immunotherapy. The risk of relapse is greater in patients who had very severe (near-fatal) anaphylaxis before VIT, elevated baseline serum tryptase level, HB allergy, or a history of systemic reactions during VIT (to venom injections or stings). The level of venom specific IgE, by skin or serum tests, does not predict the chance of relapse after stopping VIT; sting reactions have occurred in patients who had negative venom skin test results before stopping VIT.

Prevention

For optimal prevention we would need a screening test to identify individuals at risk for severe sting reactions, especially because half of fatal sting reactions occur in people who had no prior history of abnormal sting reactions. In history-negative individuals, venom specific IgE tests have limited positive predictive value. Those who have had systemic reactions to stings have a greater risk; they should get an epinephrine autoinjector prescription and should be referred to an allergist for review of the detailed history, appropriate diagnostic tests, and optimal advice for treatment and prevention. These 2 recommendations are unfortunately not followed in most emergency departments.[51] Part of the problem is a lack of awareness by emergency and primary care physicians that VIT exists, provides rapid and almost complete protection, and is curative in most cases.

Prescribing epinephrine autoinjectors for patients at low risk for severe reactions to stings requires discussion with the patient about the relatively small chance of a severe reaction and the necessity for carrying epinephrine. The quality of life is not improved with epinephrine injectors as it is with VIT, even in those with mild cutaneous reactions. In fact, many patients feel more worried about severe reactions when the physician recommends an epinephrine injector. The chance of needing epinephrine for a sting reaction is almost 1% in random adults and only 2% to 3% in large local reactors, children with cutaneous systemic reactions, patients undergoing VIT, and those who discontinue VIT after 5 years and have no high-risk factors. Patients who feel reassured by having the epinephrine may benefit from a prescription.[16]

Conclusion

Continued advances in the diagnosis and management of insect sting allergy have benefited a greater number of affected individuals, while helping to identify more accurately those who do or do not need VIT. Further research is needed to improve our ability to identify those at highest risk, to improve the induction of tolerance in high-risk patients, and to identify those who have achieved sufficient tolerance to stop treatment with negligible risk of relapse.

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